Gene Therapy in PR China: Regulations and Ethical Concerns

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Abstract: In 2003, China became the first country in the world to approve a commercial gene therapy product. Yet serious moral doubts have been raised about the conduct of the experiment. The paper examines the ethical issues (e.g. review mechanism, family consent, and therapeutic misconception) in gene therapy in Chinese culture. It argues that China should review the clinical protocols more stringintly. One reason leading to therapeutic misconception is that investigators prefer to use the term 'gene therapy' rather than 'human gene transfer research' in the consent process. Family consent, from the point of view of the author, is not in itself sufficient to justify the experimental use of patients. Family-based individual consent could be a better option, especially if there are disagreements between a patient and his family in the consent process.

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Introduction: The first commercial gene therapy product approved in China

On October 16, 2003, a Chinese company, SiBiono Gen Tech, obtained a drug license from the State Food and Drug Administration (SFDA) in China for its recombinant Ad-p53 gene therapy for head and neck Squamous Cell Carcinoma(HNSCC). This is the first commercial gene therapy production in the world. However, it does not indicate that China holds a leading position in the field of gene therapy. In fact, the scientific basis of gene therapy in China is quite "weak and thin". till 2003, only three protocols have been permitted for clinical trials in the mainland China.1

The development of clinical trials involving somatic gene therapy requires consideration of a variety of ethical issues. Many international critics speculate as to why Chinese gene therapists have been able to take such a significant step in this highly competitive field. Some opine that it has been possible because of the ease to recruit the required numbers of cancer patients in a short time because patients probably do not have access to other clinical options. Some argue that the Chinese regulatory process is much more lax in China than elsewhere. However, CEO of SiBiono Gen Tech, Peng Zhaohui, denies that Genedicine approval was because of allegedly looser regulation by the Chinese authorities.2

In this paper, I will not simply address the question whether or not SFDA should approve the gene therapy product, Genedicine. Instead, I will introduce some background regulatory information and address several ethical issues in the process of gene therapy clinical trials in China. Three serious ethical issues in the field of gene therapy clinical trials are examined here. First, should clinical protocols ever be reviewed less than stringently? Second, what are the advantages and disadvantages of family-based consent? Finally, what causes the therapeutic misconceptions in the procedure of informed consent?

Loose review vs. strict review

China was the first Asian country to conduct gene therapy clinical trials. Investigator, Jinglun Chao from Fudan University in Shanghai city led a clinical trial for Hemophilia B in 1991.3 At that time, gene therapy was a totally new concept and practice both in China and in the globe. Undoubtedly, the first attempt has aroused many ethical-regulatory concerns about the long-term safety and efficacy of the clinical trial, about the viability of consent. It also has raised questions about the acceptable risk-benefit ratio and the fair procedure of recruitment. Chinese regulatory agencies have to decide whether or not a special review mechanism is needed to handle those ethical issues and thus regulatory problems.

In fact, Chinese health authorities paid more attention to the potential regulatory issues while gene therapy clinical trials emerged in China. For example, the Ministry of Health (MOH) had voiced concerns about the eligible procedure of human gene intervention soon after the first Hemophilia B gene therapy protocol conducted in Shanghai. The MOH published the document "Point to Consider in Human Somatic Cell Therapy and Gene Therapy

Clinical Research" in 1993 which followed the lead of the United States in this field.4 The MOH regulation mainly mentioned a scientific review process explicitly for evaluating clinical applications. Although the document has a paragraph about the ethical consideration,

it says little about how to protect the welfare of human subjects. In other words, it gives the investigators and Ethical Review Committees (ERC's) very little amount of useful information from the ethical aspect. Actually, none of the ethical guidelines available in the early 1990s addressed the ethical issues in gene therapy clinical trials. There were few specific guidelines on how to select human subjects in a fair and transparent manner. There was little emphasis on the process of informed consent. Furthermore, in the early 1990s the whole ethical review system for biomedical research was in flux. For instance, a handful of hospitals and health institutions at that time had ERCs or something similar.

The number of preclinical trials in gene therapy grew rapidly in the late 1990s and some PI's such as Dr. Zhaohui Peng planned clinical applications. Meanwhile, the regulation system on biomedicine itself has evolved step by step. In 1999, the Director of SFDA, Xiaoyu Zheng, promulgated Drug Clinical Trial Administration Norms. The Administration stipulated that any drug (e.g. gene therapy products) to be marketed in China had to be conducted in an authorized Center for Pharmaceutical Clinical Trial, and the protocol must be reviewed by the local ERC's. SFDA reviews trial for medical and scientific soundness and local ERCs for ethical and medical consideration. Therefore, any gene therapy protocol covering the experimental gene and vector should file an investigational new drug (IND) application. Therefore, the gene therapy clinical trials were under dual oversight by both MOH and SFDA. However, if the cooperation between those two health authorities is so well that the dual regulation mechanism may not work well. For example, as SFDA handles the IND in a routine manner. Some gene therapy clinical research may escape special review from SFDA.

Following the death of Mr. Gelsinger, the first human subject died directly from the gene therapy clinical trials in 1999,5 China's Ministry of Science and Technology held the top-level Xiangshan Scientific Submit Conference on gene therapy in late 1999. The majority of top gene therapists and policy makers on human gene intervention joined in. Some argued that China should relax the review procedure on gene therapy, for fear of losing competitive advantages and then losing the opportunity to catch up with the latest developments in this new field. Others suggested that different protocols should be treated differently. If similar protocols have been proved to be safer abroad, we could shorten the tough review procedure. However, most of the scientists and policy makers insisted that ethical review is a crucial step not only to protect patients, but for the good name of our nation especially in the international cooperation. Therefore, a practical question is that whether China should review the gene therapy clinical protocols in a loose way.

I personally agree with the strict review approach in gene therapy clinical trials. Many a scientist lacks the awareness about the ethical review in biomedical research, so that without a strict review process misuse or exploitation of human subjects is possible. The fundamental weakness in the current review system attribute to the violation of human subject's welfare and benefit. Just because of the few clinical trails conducted in China, it is definitely set a strictly ethical requirement at the early beginning. Most importantly, there are unique reasons to hold a strict review mechanism in the special area of gene therapy, say the potential therapeutic misconception will mislead the patients and their families to make wrong decisions in the clinical settings.

The form of therapeutic misconception lies in the misuse between 'gene therapy' and 'human gene transfer clinical trial'.6 Literally, it is easy for the potential human subjects and their family to say something about the difference between those two scientific terms. For

example, the primary goal of gene therapy is to relieve the patients' suffering and restore them to health, while a clinical trial is supposed to acquire a better understanding of the bio-chemical and genetic processes involving human functioning. It is well known in the research community that 'gene therapy' is merely a kind of medical research. For instance, by the end of the year of 2003, less than 3 percent of clinical trials in the global level entered into phase III. However, not all patients hold a clear idea about the experimental nature of gene therapy at current situation. If the investigators fail to inform the potential subjects enough about the difference between research and therapy, it is possible of misuse or exploitation. For instance, many patients may agree to enroll in a gene therapy clinical trial because they are attracted by the potential for a one-time treatment as told by the investigators. Therefore, it may be more suitable to use the term 'gene therapy clinical trial' or 'human gene transfer research' in the public media and other publication, not mentioned in the process of informed consent.

It is worth discussing the role of media in the development of gene therapy in China in more detail. Human subjects and patients obtain the necessary information from informal channels: medical advertisings and scientific news in media rather than systematic training and education. The value of media in spreading new knowledge is obvious. For example, the media, especially the internet, have spread news of the approval of commercial gene therapy product in China's SFDA over night. Sometimes, however, the news or other information in media may be misleading or deceptive. For example, a medical advertising in 2002 said that experts in a traditional Chinese medicine hospital developed an innovative gene therapy for hepatitis B. It reads as follows: "hepatitis B gene therapy may not be the unique means, but it is the best one." This medical advertising overstates its therapeutic benefits, but it failed to mention any unpleasant harms or potential risks in gene therapy. As we all know, no gene therapist has developed a satisfactory gene therapy clinical trial for hepatitis B, let alone the therapeutic benefit to the patients. Obviously, this is a false and illegal medical advertising not only because it overstates the risk-benefit ration, but also because it is not gene therapy at all.

The role of family in the consent process

The idea of informed consent was a conceptual cornerstone of the Nuremberg Code which clearly states: "The voluntary consent of the human subject is absolutely essential." The Declaration of Helsinki has identified four elements of valid consent: voluntary, legally competent, informed, and comprehending. But Chinese culture and moral traditions, represented by Confucianism, are customarily described as communitarian-oriented or family-oriented rather than liberal individualism-oriented. Some argue that based on the "cultural difference argument or thesis", the Western concept of informed consent may not be applicable to China, whose cultural and ethical traditions are often conspicuously different from those of the West. Others say this thesis has ignored the fact of cross-cultural communication and the ability to integrate or coexist within Chinese local cultures.7

In fact, informed consent has been a practical moral guidance for medical research in China since the middle 1990s. For example, MOH enforced the "Guidelines on Ethical Review of Medical Research" in 1998, which required that all biomedical research involving human subjects must obtain written informed consent from human subjects. Obviously, for the policy makers, informed Consent is expected to be an essential and indispensable moral and legal prerequisite in clinical trials. The well-executed informed consent is the most important mechanism in clinical trials for ensuring patient protection from inherent risks,

unrealistic expectations, and potential conflicts of interest. In fact, protecting subjects and free decisions could not be isolated from the manifold cultural and social dominants and customs. Therefore, there is disagreement on who has the legal as well as the moral right to make consent: the individual patient or other family member? The regulation on gene therapy clinical trials in 1999 provides a different version from MOH's requirement in 1998.

In 1999, SFDA published the document: "Guideline for Application of Clinical Trial in Human Gene Therapy" which requires that: 1) patients must be informed about the procedures, benefits and risks of the protocol; 2) patients must be ensured to have the right to select or give up the protocol; 3) the family members of the patient should understand the whole protocol and give a written consent. What interested us most is that, unlike the above MOH regulation in 1998, SFDA requests the family consent rather than patient's individual consent. Why does SFDA choose the family consent instead of the individual consent? What are the advantages and disadvantages of family consent?

Individual autonomy and consent in China should not be seen as an absolute doctrine as claimed as the Nuremberg Code. Most of the assumptions implicit in a Western autonomy-based approach may not be shared by Chinese people. In Confucian culture, many people may think that individual consent may not be the most appropriate option. Informed consent is a complex process and not just a simple document which needs to be filled, as many Chinese PIs and patients think. It is hard for lay people to know the implications of scientific terms such as gene transfer, viral vector, clinical trial, etc. In-depth communication among PIs, patients, and the family ought to be encouraged anyway. However, because of possible tensions between physicians and patients, many patients sometimes distrust the physician/investigator. It is unusual for a patient to make major medical decision himself. The patient is ready to discuss his problem with those whom he trusts most. Generally speaking, family members are the frequent choice. It is an important precondition for family participation and collective decision.

There are definitely advantages of the concept of family consent. The individual is not isolated from the social interpersonal relationships. Patients live amidst concrete human relationships. This is probably more realistic and human than the Western view as purely rational, autonomous, right-bearing individuals. These relationships were important because patients would naturally feel at ease with this way in decision making. The core value of Confucian ethics is Ren (humanity); one of its complicated meanings is the human relationship. Family participating in clinical decision making may be seen as a kind of care and respect for the patient. Family members do not want the patient himself share the burden of fear and unease. Second, the family helps the subjects to confront all kinds of difficulties and give economic and emotional support. It is customary for a male family member, such as the father or grandfather to make the decision. The reason for this is not only the traditional male centered culture where men always are the opinion leaders, but patients also feel only the family members are worth trusting. In many cases, a physician/investigator prefers to tell the patient's family the "true story" and let them decide.

A kind of family-sovereignty seems to be predominant in medical settings as it is in daily Chinese life. The linkage between family-centered culture and medical practices in China drives us to regard and respect the family as an admirable virtue which is contrasted to "Western atomistic individualism".8 The particular case at point is that Chinese physicians prefer to break bad news about a patients cancer to his family rather than tell the patient directly. Researchers choose to discuss with the family about whether or not the patients

could enroll in the clinical trial. Without the consent of the family, physician/investigators will not enroll a patient into a gene therapy clinical trial.

In a broad sense, Confucian thought maybe encourages a kind of weak paternalism. Mencius says that humans are not distinguishable from animals if they do not have a concept of father and king. This means that a Confucian patient cannot and need not free himself from the bonds of certain social relationships. Within the Confucian conceptual framework, some of the distinctions essential in Western philosophy such as those between public life and private life are simply not drawn. If the family acts in the benefit of patient/subject, Confucians believe it may helps to gain a desirable harmony within social bounds based on mutual concern. An independent choice may be not alien to the Confucian moral person.9 A morally ideal person in a Confucian context is characterized by independent choices, by the exercise of will and voluntarism.

Family-based individual consent

There are problems with family consent in practice. The first problem is: Which family makes a decision for the human subject? It goes without saying that parents could make proxy consent for their children in the clinical trials setting. Even so, many times, the ERCs require the assent from the child if available. It is also little disagreement in the traditional family structure that adult males give the informed consent because man's position is higher than women's in that culture. However, in modern society, things changed. Women, especially those who are economically independent, may have the equal power in decision making. Therefore, it raises the question: who should represent the family?

If family members participate in the decision making process, the potential problem is that this may violate the privacy of human subjects. Gene therapy clinical trials involve different personal genetic information, some of which may be shared by other family members or patients. Such genetic information may include the nature of genetic disease, the way of heritage, and the seriousness of the disease. When a family member decides to be a voluntary participant, others may hold a strong interest in the whole consent process. In the open discussion about whether a family member should be enrolled in a clinical trial, possibly the identified personal or family genetic information will disclose.

Family consent may permit the violation of the right of human subjects if there are disagreement between him and the family. Obviously, according to the SFDA's regulation in 1999, if a patient's family members make a written consent, then the patient has the obligation to participate. What happens if the patient himself disagrees with family decision? Consider the following case: Suppose a woman from a rural area developed later cancer. The husband has borrowed money for her treatment, but the regional hospital could do nothing helpful. Then they went to the capital Beijing for seeking better treatment. The physician of a famous cancer hospital told the couple that the patient had two alternatives: one is the conventional radiotherapy; the other is the cancer gene therapy clinical trial. The patient herself prefers to join the clinical trial because it is not only free of charge, but it may offer the last chance for her suffering. Considering the uncertainty of the therapeutic benefit and potential risks in the gene therapy clinical trials, the husband is inclined towards radiotherapy. In this case, the husband's consent does not represent the will of patient herself. The patient herself may be deprived of her/his autonomy. Obviously, the SFDA's regulation does not provide a appropriate solution.

In 2003, SFDA published ”Principles on Human Gene Therapy Research and Product Quality Control”. It stated that only after the signature of patients and his/her family members in the consent form that should the trial be conducted. SFDA changed the requirement as to increase the legal right of the patient himself. However, the new version cannot solve the above problem as well . In my opinion, we need a individual consent qualified as a genuine (moral) choice in one hand, we also need the participation of the whole family in the other hand As a solution, family-based individual consent would be a good approach. In this way, we do not deny the role of family involved in the consent process considering Chinese culture and traditions. And we may not necessary violate the right of individual autonomy. Although the vocabulary of autonomy may be absent from the Confucian way of thinking about persons, it does not mean that the human subject under the help of family is not autonomous. In Confucian ethics, choice is important in the sense that morality depends on a choice independent of one's consideration of benefits because only in that way the status of morality and the dignity of a moral person can authentically emerge.10 In Confucian thought, the morally excellent men are able to achieve an autonomous inner equanimity, as well as an outer integrity. Confucian ethics respect the inner value of the individual. Western traditions have required people to overcome their sense of dependence and to achieve self-control. In contrast, in China there is the cultural-specific form of the principle of autonomy that upholds the value of harmonious dependence. It should be emphasized that family members involved in the decision making process may not necessary belittle individual autonomy and voluntary choice. However, if there is a disagreement between patient and the family, only the patient himself has the legal right to make the final consent. In my view, the family-based individual consent is the better approach.

Conclusion

Chinese experts and policy makers have realized the importance of the ethical, legal and social implications (ELSI) of gene therapy after the event of Gelsinger's death. For example, the Committee of Beijing's Science of Technology supported a research project on the ELSI of gene therapy in 2001. This is the first time that China´s Government funded the ELSI of gene therapy. It is a great start on the research capacity of ELSI related to gene therapy. The ELSI studies in China should not just follow what have been fully discussed in the western culture. For example, while the 'Play God' argument or thesis is popular in Judeo-Christian culture, few Chinese bioethicists argue in this dimension, partly because the talk about "playing God" itself is somehow unfamiliar to many Chinese scholars .11 I hope scholars rooted in the Chinese culture may make special contribution to the world.

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